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## Carbamazepine for chronic neuropathic pain and fibromyalgia in adults (Review)

Wiffen PJ, Derry S, Moore RA, Kalso EA

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## [Intervention Review]

# Carbamazepine for chronic neuropathic pain and fibromyalgia in adults

Philip J Wiffen<sup>1</sup>, Sheena Derry<sup>2</sup>, R Andrew Moore<sup>3</sup>, Eija A Kalso<sup>4,5</sup>

<sup>1</sup>Thame, UK. <sup>2</sup>Oxford, UK. <sup>3</sup>Plymouth, UK. <sup>4</sup>Institute of Clinical Medicine, University of Helsinki, Helsinki, Finland. <sup>5</sup>Department of Anaesthesia, Intensive Care and Pain Medicine, Helsinki University and Helsinki University Hospital, Helsinki, Finland

**Contact:** Philip J Wiffen, Thame, UK. [pwiffen@oxfordsrs.org.uk](mailto:pwiffen@oxfordsrs.org.uk).

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## ABSTRACT

### Background

This is an update of a Cochrane review entitled 'Carbamazepine for acute and chronic pain in adults' published in Issue 1, 2011. Some antiepileptic medicines have a place in the treatment of neuropathic pain (pain due to nerve damage). This updated review considers the treatment of chronic neuropathic pain and fibromyalgia only, and adds no new studies. The update uses higher standards of evidence than the earlier review, which results in the exclusion of five studies that were previously included.

### Objectives

To assess the analgesic efficacy of carbamazepine in the treatment of chronic neuropathic pain and fibromyalgia, and to evaluate adverse events reported in the studies.

### Search methods

We searched for relevant studies in MEDLINE, EMBASE and CENTRAL up to February 2014. Additional studies were sought from clinical trials databases, and the reference list of retrieved articles and reviews.

### Selection criteria

Randomised, double blind, active or placebo controlled trials (RCTs) investigating the use of carbamazepine (any dose, by any route, and for at least two weeks' duration) for the treatment of chronic neuropathic pain or fibromyalgia, with at least 10 participants per treatment group. Participants were adults aged 18 and over.

### Data collection and analysis

Two study authors independently extracted data on efficacy, adverse events, and withdrawals, and examined issues of study quality. Numbers needed to treat for an additional beneficial effect (NNT) or harmful effect (NNH) with 95% confidence intervals (CIs) were calculated from dichotomous data.

We performed analysis using three tiers of evidence. First tier evidence derived from data meeting current best standards and subject to minimal risk of bias (outcome equivalent to substantial pain intensity reduction, intention-to-treat analysis without imputation for dropouts, at least 200 participants in the comparison, at least 8 weeks' duration, parallel design), second tier from data that failed to meet one or more of these criteria and were considered at some risk of bias but with adequate numbers in the comparison, and third tier from data involving small numbers of participants that was considered very likely to be biased or used outcomes of limited clinical utility, or both.

## Main results

Ten included studies (11 publications) enrolled 480 participants with trigeminal neuralgia, diabetic neuropathy, and post stroke pain. Nine studies used a cross-over design, and one a parallel group design. Most of the studies were of short duration, lasting four weeks or less.

No study provided first or second tier evidence for an efficacy outcome. Using third tier evidence, carbamazepine generally provided better pain relief than placebo in the three conditions studied, with some indication of pain improvement over mainly the short term, but with poorly defined outcomes, incomplete reporting, and in small numbers of participants. There were too few data in studies comparing carbamazepine with active comparators to draw any conclusions.

In four studies 65% (113/173) of participants experienced at least one adverse event with carbamazepine, and 27% (47/173) with placebo; for every five participants treated, two experienced an adverse event who would not have done so with placebo. In eight studies 3% (8/268) of participants withdrew due to adverse events with carbamazepine, and none (0/255) with placebo. Serious adverse events were not reported consistently; rashes were associated with carbamazepine. Four deaths occurred in patients on carbamazepine, with no obvious drug association.

## Authors' conclusions

Carbamazepine is probably effective in some people with chronic neuropathic pain, but with caveats. No trial was longer than four weeks, had good reporting quality, nor used outcomes equivalent to substantial clinical benefit. In these circumstances, caution is needed in interpretation, and meaningful comparison with other interventions is not possible.

## PLAIN LANGUAGE SUMMARY

### Carbamazepine for chronic neuropathic pain and fibromyalgia in adults

Neuropathic pain is pain coming from damaged nerves. It is different from pain messages carried along healthy nerves from damaged tissue (a fall, or cut, or arthritic knee). Neuropathic pain is treated by different medicines than pain from damaged tissue. Medicines like paracetamol or ibuprofen are not effective in neuropathic pain, while medicines that are sometimes used to treat depression or epilepsy can be very effective in some people. Our understanding of fibromyalgia (a condition of persistent, widespread pain and tenderness, sleep problems, and fatigue) is lacking, but fibromyalgia can respond to the same medicines as neuropathic pain.

Carbamazepine was developed to treat epilepsy, but it is now used to treat various forms of chronic pain. We performed searches (up to February 2014) to look for clinical trials where carbamazepine was used to treat neuropathic pain or fibromyalgia. We found 10 studies involving 418 people involved in testing carbamazepine. Studies were not generally of very good quality. Most were very small, as well as of short duration. Studies lasting only one or two weeks are unhelpful when pain can last for years.

There was not enough good quality evidence to say how well carbamazepine worked in any neuropathic pain condition. Pooling four small studies showed that it was better than placebo, but the result cannot be relied upon. There was not enough information from these studies to make any reliable comment on adverse events or harm.

Carbamazepine is probably helpful for some people with chronic neuropathic pain. It is not possible to know beforehand who will benefit and who will not.

## SUMMARY OF FINDINGS

### Summary of findings for the main comparison.

#### Carbamazepine compared with placebo for chronic neuropathic pain

**Patient or population:** adults with neuropathic pain (Trigeminal neuralgia, painful diabetic neuropathy, chronic post stroke pain)

**Settings:** community

**Intervention:** oral carbamazepine (100 mg to 2400 mg daily)

**Comparison:** placebo

Outcomes	Probable out- come with placebo	Probable out- come with in- tervention	NNT or NNH and/ or relative effect (95% CI)	No of partici- pants and studies	Quality of the evidence (GRADE)	Comments
"Substantial" benefit At least 50% reduction in pain or equivalent	94 in 1000	608 in 1000	RR 6.5 (3.4 to 12)  NNT 1.9 (1.6 to 2.5)	188 participants,  4 studies	Low	Mixed conditions and doses, small studies of short duration, imputation not reported
"Moderate" benefit At least 30% reduction in pain	No data				Very low	No data
Proportion below 30/100 mm on VAS	No data				Very low	No data
Patient Global Impression of Change much or very much im- proved	No data				Very low	No data
Any adverse event	270 in 1000	660 in 1000	RR 2.4 (1.9 to 3.2)  NNH 2.6 (2.1 to 3.5)	346 participants,  4 studies	Low	Cross-over studies  Denominator = all <b>potentially</b> ex- posed
Adverse event withdrawals	0 in 1000	30 in 1000	not calculated	523 participants,  8 studies	Very low	Cross-over studies  Denominator = all <b>potentially</b> ex- posed
Serious adverse events	not reported	3	not calculated	46 participants,	Very low	Denominator = all <b>potentially</b> ex- posed

				2 studies		
Death	not reported	4	not calculated	44 participants 1 study	Very low	Denominator = all <b>potentially</b> exposed

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

NNT: number needed to treat for an additional beneficial effect; NNH: number needed to treat for an additional harmful effect; RR: risk ratio; VAS: visual analogue scale.

## BACKGROUND

This updated review was originally published in *The Cochrane Library* as 'Anticonvulsant drugs for acute and chronic pain' (Wiffen 2000). At the third update in 2003 (Wiffen 2003), 12 new included studies were identified mainly of the newer antiepileptics (anticonvulsants) gabapentin and lamotrigine. In total the included studies provided data on six different medicines used in at least six identified neuropathic pain conditions. Issues of dose response and trial design added to the complexity. A decision was therefore taken to split that review into a number of smaller reviews each covering one medicine (chemical entity). In 2010 a review of carbamazepine for acute and chronic pain was published, and in 2011 the authors reviewed the literature and concluded that there were unlikely to be any new studies, so the review was marked as stable (Wiffen 2011a).

The decision to update it now, and concentrate on chronic neuropathic pain and fibromyalgia, was made because there have been more advances in the rigour with which we assess studies and report data, and in order to conform with other reviews in the series on neuropathic pain and fibromyalgia. In particular we consider study size and duration, outcomes reported, and method of imputation for withdrawals, and report results in three tiers according to outcome and freedom from known sources of bias. We wanted to bring this review in line with a template protocol so that it can be easily included in overview of antiepileptics for chronic neuropathic pain and fibromyalgia in adults (Wiffen 2013a). Reviews of clonazepam (Corrigan 2012), gabapentin (Moore 2011), lacosamide (Hearn 2012), lamotrigine (Wiffen 2013b), oxcarbazepine (Zhou 2013), phenytoin (Birse 2012), pregabalin (Moore 2009a), topiramate (Wiffen 2013c), and valproic acid (Gill 2011) have been completed. All the reviews analyse results according to the particular conditions in which they have been studied, and it is expected that in future updates fibromyalgia, at least, will become the subject of separate reviews.

The aim is for all our reviews to use the same methods, based on new criteria for what constitutes reliable evidence in chronic pain (Moore 2010a; Moore 2012b; Appendix 1). A Cochrane review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009a). This indicates that different neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good grounds for doing so. While fibromyalgia is considered to have a different aetiology from chronic neuropathic pain, it is a condition that responds to the same therapies. Because of limitations in the number of available clinical trials, it is convenient to consider fibromyalgia together with neuropathic pain. We make no presumption to pool data across individual neuropathic pain conditions or fibromyalgia, but will consider each condition separately.

The small amount of information in the 2011 review relating to acute pain has been moved to Appendix 2.

### Description of the condition

The 2011 International Association for the Study of Pain definition of *neuropathic pain* is "pain caused by a lesion or disease of the somatosensory system" (Jensen 2011) based on an earlier

consensus meeting (Treede 2008). Neuropathic pain may be caused by nerve damage, but is often followed by changes in the central nervous system (CNS) (Moisset 2007). It is complex, and neuropathic pain features can be found in patients with joint pain (Soni 2013).

*Fibromyalgia* is defined as widespread pain for longer than three months with pain on palpation at 11 or more of 18 specified tender points (Wolfe 1990), and is frequently associated with other symptoms such as poor sleep, fatigue, and depression. More recently, a definition of fibromyalgia has been proposed based on symptom severity and the presence of widespread pain (Wolfe 2010). The cause, or causes, are not well understood, but it has features in common with neuropathic pain, including changes in the CNS. Moreover, patients with neuropathic pain and those with fibromyalgia experience similar sensory phenomena (Koroshetz 2011), and peripheral nerve fibre changes seen in neuropathic pain also occur in fibromyalgia (Oaklander 2013; Üçeyler 2013). Many people with these conditions are significantly disabled with moderate or severe pain for many years.

In primary care in the United Kingdom (UK), the incidences per 100,000 person-years' observation have been reported as 28 (95% CI 27 to 30) for postherpetic neuralgia, 27 (26 to 29) for trigeminal neuralgia, 0.8 (0.6 to 1.1) for phantom limb pain, and 21 (20 to 22) for painful diabetic neuropathy (Hall 2008). Estimates vary between studies, often because of small numbers of cases. The incidence of trigeminal neuralgia has been estimated at 4 in 100,000 per year (Katusic 1991; Rappaport 1994), while more recently, a study of facial pain in The Netherlands found incidences per 100,000 person-years of 12.6 for trigeminal neuralgia and 3.9 for postherpetic neuralgia (Koopman 2009). A systematic review of chronic pain demonstrated that some neuropathic pain conditions, such as painful diabetic neuropathy, can be more common, with prevalence rates up to 400 per 100,000 person-years (McQuay 2007). The prevalence of neuropathic pain was reported as being 3.3% in Austria (Gustorff 2008), 6.9% in France (Bouhassira 2008) and as high as 8% in the UK (Torrance 2006), and about 7% in a systematic review of studies published since 2000 (Moore 2013a). The incidence of some forms of neuropathic pain, such as diabetic neuropathy and postherpetic neuralgia, is increasing (Hall 2013). Fibromyalgia is common, especially in women, with an all-age prevalence of 12%, and a female to male ratio of 6:1 (McNally 2006).

Neuropathic pain and fibromyalgia are known to be difficult to treat effectively, with only a minority of individuals experiencing a clinically relevant benefit from any one intervention. A multidisciplinary approach is now advocated, with pharmacological interventions being combined with physical and/or cognitive interventions. Conventional analgesics are usually not effective. Some patients with neuropathic pain may derive some benefit from topical lidocaine patch or low concentration topical capsaicin, although evidence of benefit is uncertain (Derry 2012; Khaliq 2007). High concentration topical capsaicin may benefit some patients with postherpetic neuralgia (Derry 2013). Treatment is more usually by so-called unconventional analgesics such as antidepressants like duloxetine and amitriptyline (Lunn 2009; Moore 2012a; Sultan 2008) or antiepileptics like gabapentin or pregabalin (Moore 2009a; Moore 2011). The proportion of patients who achieve worthwhile pain relief (typically defined as at least 50% pain intensity reduction (Moore 2013b)) is small, typically 10%

to 25% more than with placebo, with numbers needed to treat for an additional beneficial outcome (NNTs) usually between 4 and 10.

## Description of the intervention

Carbamazepine was first marketed in the early 1960s to treat trigeminal neuralgia, with its antiepileptic effects recognised soon afterwards. It is licensed in the United Kingdom and United States of America for paroxysmal pain of trigeminal neuralgia (dosage up to 1600 mg daily), but has been used off-label for other types of neuropathic pain. It is usually prescribed as a tablet, but chewable tablet, liquid, and suppository formulations are manufactured.

Antiepileptic drug use is not without risk: serious adverse effects have been reported, including deaths from haematological reactions (blood dyscrasias; [Sweetman 2005](#)), and life-threatening cutaneous problems ([Chung 2010](#); [Kulkantrakorn 2012](#)). Carbamazepine is also known to stimulate synthesis of certain enzymes, which can interfere with other drug therapies (e.g. anticoagulants, antiretrovirals, statins, antihypertensives) causing clinical problems, particularly at initiation and withdrawal ([Brodie 2013](#)). The most common adverse effects are impaired mental and motor function, which may limit clinical use, particularly in older people ([Grahame-Smith 1992](#); [Rall 1992](#); [Sweetman 2005](#)).

## How the intervention might work

Pain that manifests in different diseases may operate through common mechanisms, but the same symptom in two patients may be caused by different mechanisms. It is therefore impossible to predict the mechanisms responsible for an individual's pain based on the aetiology of the neuropathy or on the distribution or nature of symptoms ([Woolf 1999](#)). Carbamazepine stabilizes the inactivated state of voltage-gated sodium channels, so that fewer of these channels are available to open, and brain cells are less excitable and less likely to fire ([Ambrósio 1999](#); [Morisset 2013](#)).

## Why it is important to do this review

The standards used to assess evidence in chronic pain trials have changed substantially in recent years, with particular attention being paid to trial duration, withdrawals, and statistical imputation following withdrawal, all of which can substantially alter estimates of efficacy ([Appendix 1](#)). The most important change is the move from using average pain scores, or average change in pain scores, to using the number of patients who have a large decrease in pain (by at least 50%); this level of pain relief has been shown to correlate with improvements in comorbid symptoms, function, and quality of life. These standards are set out in the reference guide for pain studies ([AUREF 2012](#)) and reflect what patients with chronic pain want from treatment ([Moore 2013a](#)).

This Cochrane review will assess evidence in ways that make both statistical and clinical sense, and will use developing criteria for what constitutes reliable evidence in chronic pain ([Moore 2010a](#)). Trials included and analysed will need to meet a minimum of reporting quality (blinding, randomisation), validity (duration, dose and timing, diagnosis, outcomes, etc), and size (ideally at least 500 participants in a comparison in which the (NNT) is four or more ([Moore 1998](#))).

Carbamazepine has been used to treat some types of neuropathic pain for about 50 years. It is important to know its place in the range of drugs used to treat the various types of neuropathic pain.

This updated review brings the evidence for carbamazepine into line with that for other medicines used in these conditions, and will form part of an overview of antiepileptic drugs for chronic neuropathic pain and fibromyalgia.

## OBJECTIVES

To assess the analgesic efficacy of carbamazepine in the treatment of chronic neuropathic pain and fibromyalgia, and to evaluate adverse events reported in the studies.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included studies if they were randomised controlled trials (RCTs) with at least 10 participants per treatment group and double-blind (participant and observers) assessment of participant-reported outcomes, following two weeks of treatment or longer, although the emphasis of the review is on studies of eight weeks or longer. Full journal publication was required, with the exception of extended abstracts of otherwise unpublished clinical trials (for example detailed information from PDFs of posters that typically include all important details of methodology used and results obtained). We did not include short abstracts (usually meeting reports with inadequate or no reporting of data). We excluded studies of experimental pain, case reports, and clinical observations.

Migraine and headache studies previously included in an earlier version of this review were excluded ([Wiffen 2000](#)). This subject is being dealt with in greater depth by the Cochrane Pain, Palliative Care and Supportive Care Review Group.

#### Types of participants

We included adult participants aged 18 years and above. Participants could have one or more of a wide range of chronic neuropathic pain conditions including (but not limited to):

- painful diabetic neuropathy (PDN);
- postherpetic neuralgia (PHN);
- trigeminal neuralgia;
- phantom limb pain;
- postoperative or traumatic neuropathic pain;
- complex regional pain syndrome (CRPS) Type II;
- cancer-related neuropathy;
- HIV-neuropathy;
- spinal cord injury;

or

- fibromyalgia;
- complex regional pain syndrome (CRPS) Type I.

We also included studies of participants with more than one type of neuropathic pain. We analysed results according to the primary condition.



## Types of interventions

Carbamazepine in any dose, by any route, administered for the relief of neuropathic pain or fibromyalgia, and compared to placebo, no intervention or any other active comparator. We did not include studies using carbamazepine to treat pain resulting from the use of other drugs.

## Types of outcome measures

We anticipated that studies would use a variety of outcome measures, with the majority of studies using standard subjective scales (numerical rating scale (NRS) or visual analogue scale (VAS)) for pain intensity or pain relief, or both. We were particularly interested in Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definitions for moderate and substantial benefit in chronic pain studies (Dworkin 2008). These are defined as at least 30% pain relief over baseline (moderate), at least 50% pain relief over baseline (substantial), much or very much improved on Patient Global Impression of Change (PGIC) (moderate), and very much improved on PGIC (substantial). These outcomes concentrate on dichotomous outcomes where pain responses do not follow a normal (Gaussian) distribution. People with chronic pain desire high levels of pain relief, ideally more than 50%, and with pain intensity not worse than mild (O'Brien 2010).

We include a Summary of findings table as set out in the Cochrane Pain, Palliative and Supportive Care Group author guide (AUREF 2012). The Summary of findings table includes outcomes of at least 30% and at least 50% pain intensity reduction, PGIC, at least one adverse event, adverse event withdrawals, serious adverse events and death.

## Primary outcomes

1. Participant-reported pain intensity reduction of 30% or greater.
2. Participant-reported pain intensity reduction of 50% or greater.
3. Participant-reported global impression of clinical change (PGIC) much or very much improved.
4. Participant-reported global impression of clinical change (PGIC) very much improved.

## Secondary outcomes

1. Any pain-related outcome indicating some improvement.
2. Withdrawals due to lack of efficacy.
3. Participants experiencing any adverse event.
4. Participants experiencing any serious adverse event.
5. Withdrawals due to adverse events.
6. Specific adverse events, particularly somnolence and dizziness.

These outcomes are not eligibility criteria for this review, but are outcomes of interest within whichever studies are included.

## Search methods for identification of studies

Studies were identified by several methods.

## Electronic searches

For the earlier review, RCTs of antiepileptics in acute, chronic or cancer pain were identified by searching MEDLINE (originally via

Silver Platter, then Ovid) from 1966 to June 2010, EMBASE 1994 to Dec 2009, SIGLE 1980 to July 1999, and CENTRAL (Issue 4, 2010).

When the review was split in to individual drugs, this search strategy was narrowed to include carbamazepine only. Appendix 3 has the search strategies for CENTRAL, MEDLINE and EMBASE.

For this update we searched:

- Cochrane Central Register of Controlled Trials (CENTRAL, 2014 Issue 1 in *The Cochrane Library*);
- MEDLINE (via Ovid) (January 2010 to 7 February 2014);
- EMBASE (via Ovid) (January 2010 to 7 February 2014);
- PhRMA clinical study results database (clinicaltrials.gov) to 7 February 2014;
- WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch) to 7 February 2014

## Searching other resources

Additional studies were identified from the reference list of the retrieved papers. In the first version, a letter was sent to the first author of a report for further information on their published report (method of randomisation, double blinding, outcome measures and dropouts) and to ask if they knew of any other studies which met our inclusion criteria, either undertaken by them or by other investigators. In addition, 41 medical journals were hand searched, chosen from the 50 with the highest number of reports in MEDLINE, and nine specialist journals which were either not on that list or were not indexed (Jadad 1994). The search process included volumes published between 1950 and 1990. No further hand searching has been undertaken as the key journals are now being searched by the Cochrane Collaboration.

In an earlier version of this review data were requested from 19 authors but only one (Leijon 1989) was able to supply information relevant to this review. In the two updates, no further attempt was made to contact authors.

## Data collection and analysis

### Selection of studies

Two review authors independently read the titles and abstracts of all studies identified by the search, and the full text of all potentially relevant studies. Agreement on eligibility was reached by discussion. We did not anonymise the studies in any way before assessment.

### Data extraction and management

Two review authors extracted data using a standard data extraction form, and agreed data before entry into RevMan (RevMan 2012) or any other analysis method. Data extracted included information about the pain condition and number of participants treated, drug and dosing regimen, study design, study duration and follow up, analgesic outcome measures and results, withdrawals and adverse events (participants experiencing any adverse event, or a serious adverse event).

### Assessment of risk of bias in included studies

We independently scored each study for quality using a three-item scale (Jadad 1996) and agreed a 'consensus' score for each study. Scores of two and below have been associated with greater

estimates of efficacy than studies of higher quality (Khan 1996). Quality scores were not used to weight the results in any way.

We used the 'Risk of bias' tool to assess the likely impact on the strength of the evidence of various study characteristics relating to methodological quality (randomisation, allocation concealment, blinding, freedom from selective reporting), study validity (duration, outcome reporting, and handling of missing data), and size (Moore 2010a).

Two review authors independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We assessed the following for each study.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions before assignment determines whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (e.g. open list).
- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, e.g. identical tablets; matched in appearance and smell); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how this was achieved). We excluded studies that were not double-blind.
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk of bias (< 10% of participants did not complete the study and/or used 'baseline observation carried forward' analysis); unclear risk of bias (used 'last observation carried forward' analysis); high risk of bias (used 'completer' analysis).
- Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias ( $\geq 200$  participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (< 50 participants per treatment arm).

### Measures of treatment effect

Relative risk (or risk ratio, RR) was used to establish statistical difference. Numbers needed to treat (NNT) and pooled percentages were used as absolute measures of benefit or harm.

The following terms are used to describe adverse outcomes in terms of harm or prevention of harm:

- When significantly fewer adverse outcomes occurred with carbamazepine than with control (placebo or active) we use the term the number needed to treat to prevent one event (NNTP).
- When significantly more adverse outcomes occurred with carbamazepine compared with control (placebo or active) we use the term the number needed to harm or cause one event (NNH).

### Unit of analysis issues

The control treatment arm would be split between active treatment arms in a single study if the active treatment arms were not combined for analysis.

### Dealing with missing data

We planned to use intention-to-treat (ITT) analysis wherever possible. The ITT population consisted of participants who were randomised, took the assigned study medication and provided at least one post-baseline assessment. Missing participants were assigned zero improvement (baseline observation carried forward, BOCF) where this could be done. We were aware that imputation methods might be problematical and examined trial reports for information about them.

### Assessment of heterogeneity

We planned to deal with clinical heterogeneity by combining studies that examined similar conditions. We assessed statistical heterogeneity visually (L'Abbe 1987) and with the use of the  $I^2$  statistic.

### Assessment of reporting biases

The aim of this review was to use dichotomous data of known utility (Moore 2009b). The review did not depend on what authors of the original studies chose to report or not report, though clearly there were difficulties with studies failing to report any dichotomous results. Continuous data, which probably poorly reflect efficacy and utility, were extracted and used only when useful for illustrative purposes.

We undertook no statistical assessment of publication bias.

We looked for evidence of possible enrichment, either complete or partial, in enrolment of participants into the studies. Enrichment typically means including participants known to respond to a therapy, and excluding those known not to respond, or to suffer unacceptable adverse effects, though for gabapentin no significant effects have been shown from partial enrichment (Straube 2008). Enriched enrolment randomised withdrawal studies, known to produce higher estimates of efficacy, would not be pooled (McQuay 2008).

### Data synthesis

We analysed data for each painful condition in three tiers, according to outcome and freedom from known sources of bias.

- The first tier uses data meeting current best standards, where studies report the outcome of at least 50% pain intensity reduction over baseline (or its equivalent), without the use of last observation carried forward (LOCF) or other imputation

method for dropouts, report an intention-to-treat (ITT) analysis, last eight or more weeks, have a parallel-group design, and have at least 200 participants (preferably at least 400) in the comparison (Moore 2010a; Moore 2012b). These top-tier results are reported first.

- The second tier uses data from at least 200 participants but where one or more of the above conditions is not met (for example reporting at least 30% pain intensity reduction, using LOCF or a completer analysis, or lasting four to eight weeks).
- The third tier of evidence relates to data from fewer than 200 participants, or where there are expected to be significant problems because, for example, of very short duration studies of less than four weeks, where there is major heterogeneity between studies, or where there are shortcomings in allocation concealment, attrition, or incomplete outcome data. For this third tier of evidence, no data synthesis is reasonable, and may be misleading, but an indication of beneficial effects might be possible

### Subgroup analysis and investigation of heterogeneity

We planned for all analyses to be according to individual painful conditions, because placebo response rates with the same

outcome can vary between conditions, as can the drug-specific effects (Moore 2009a). We also planned subgroup analysis for dose of carbamazepine and duration of study.

### Sensitivity analysis

We planned no sensitivity analyses because the evidence base was known to be too small to allow reliable analysis.

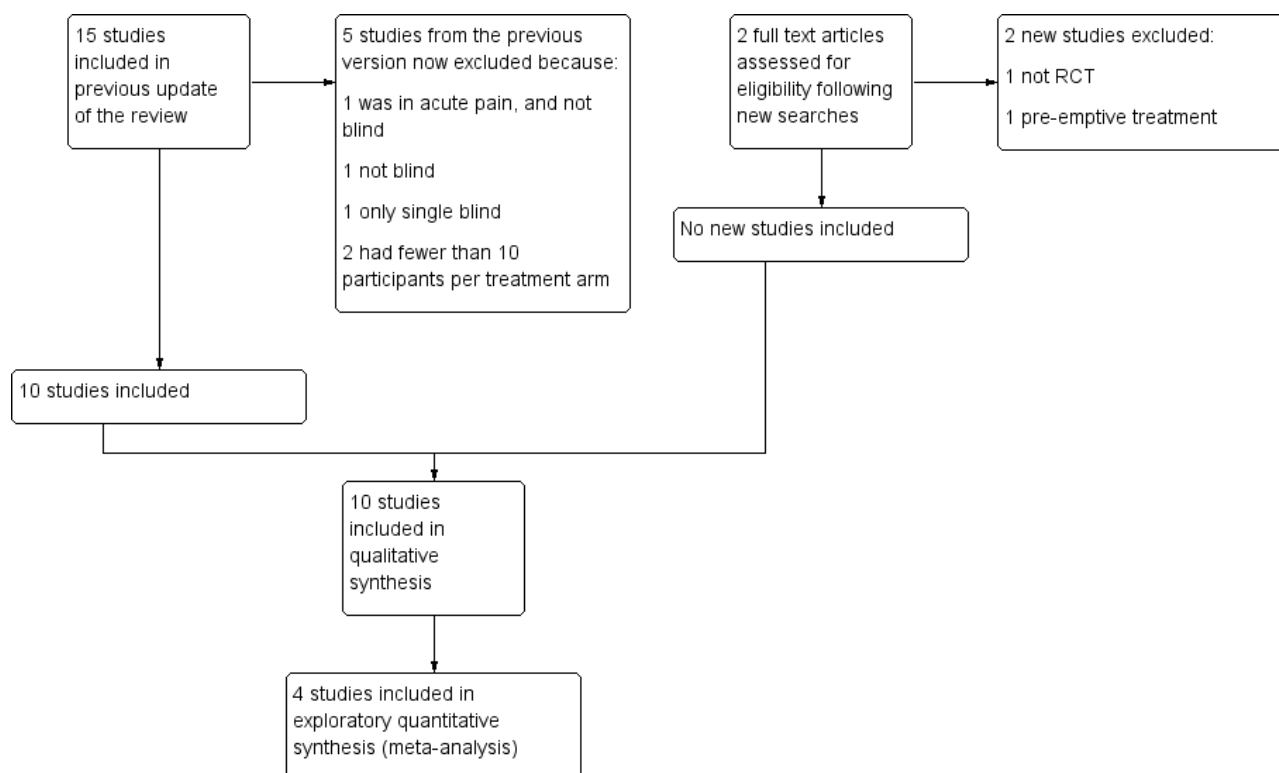
## RESULTS

### Description of studies

#### Results of the search

New searches to February 2014 identified two potentially relevant studies (Salinas 2012; Shaikh 2011), but neither satisfied our inclusion criteria, so there were no new included studies in this update. Two studies that were identified in an earlier search remain unavailable (Badran 1975; Liebel 2001). Figure 1 shows the flow diagram for included studies.

**Figure 1. Study flow diagram.**



### Included studies

This updated review includes 10 studies (11 publications) with 480 participants, 414 of whom were randomised to receive carbamazepine, although not all of them contributed to analyses. Three studies (Gomez-Perez 1996; Jia 2006; Nicol 1969) did not report the age or sex, or both, of participants, but in the remaining studies the mean age was 52 to 59 years (range 20 to 84 years), and the majority of participants were female.

A wide range of carbamazepine doses, ranging from 100 mg to 2400 mg daily, were used in the studies. Cross-over studies predominated; only one had a parallel group design (Jia 2006). Most of the studies were of short duration, lasting four weeks or less. Pain conditions studied were trigeminal neuralgia, painful diabetic neuropathy, and post stroke pain.

Many of the studies were relatively old, with five published in the 1960s. Only one study (Jia 2006) has been published in

the last ten years. A consequence of the age of the studies is that outcomes - pain, adverse event, and discontinuation - were reported inconsistently. Pooling of trial data in meta-analyses was therefore problematical, because few studies reported the same outcomes in the same way in the same condition.

Details of included studies are given in the '[Characteristics of included studies](#)' table.

### Excluded studies

Five studies that were included in the earlier reviews are now excluded:

- one in acute herpes zoster ([Keczkes 1980](#)) due to the change of title to chronic pain and it was probably not blinded,
- one in postherpetic neuralgia ([Gerson 1977](#)) because it was not blinded, and

- three in trigeminal neuralgia: one ([Rasmussen 1970](#)) because it was only single blind, and two ([Rockliff 1966](#); [Vilming 1986](#)) because they had fewer than 10 participants per treatment arm.

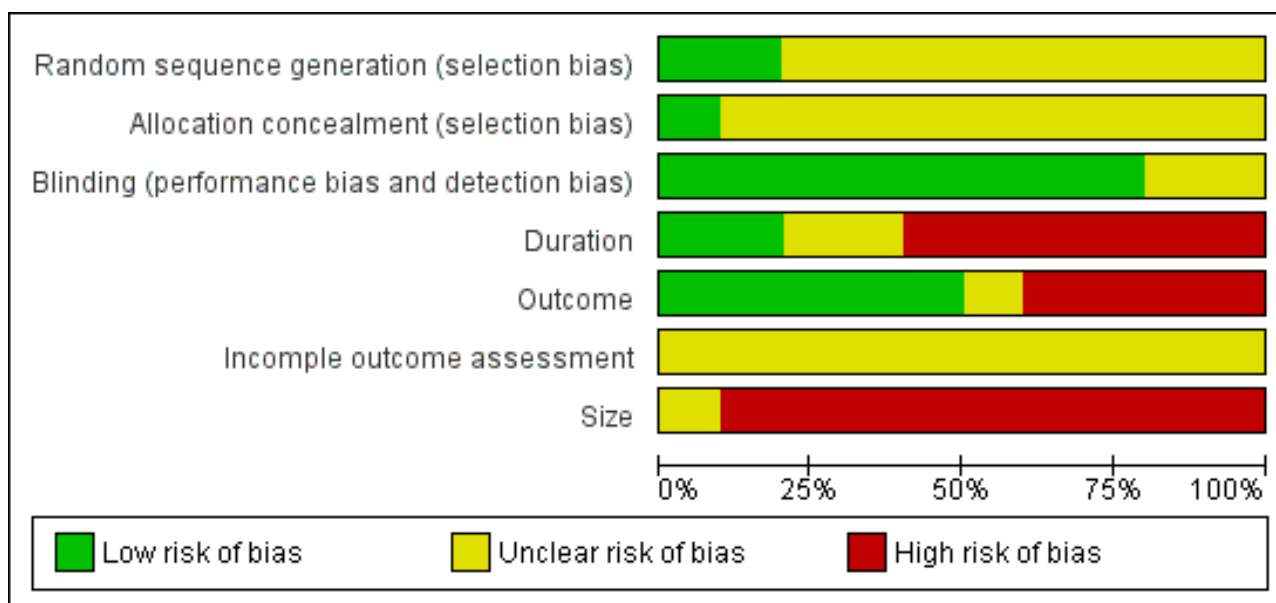
Details of included studies are given in the '[Characteristics of excluded studies](#)' table.

### Risk of bias in included studies

Out of a maximum of five points, two studies scored 5 points, five scored 4 points, one scored 3 points, and two scored 2 points on the Oxford Quality Scale. Points were lost due to failure to adequately report withdrawals or details of the randomisation and blinding processes. Scores for individual trials are reported in the notes section of '[Characteristics of included studies](#)' table.

A risk of bias table was completed for randomisation, allocation concealment and blinding ([Figure 2](#); [Figure 3](#)). All the included studies were judged to be at high risk of bias from at least one of three potential sources relating to size, duration, and outcome:

**Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**



**Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Duration	Outcome	Incomplete outcome assessment	Size
Campbell 1966	+	?	+	-	-	?	-
Gomez-Perez 1996	?	?	+	?	+	?	-
Jia 2006	+	+	+	-	-	?	?
Killian 1968	?	?	+	-	+	?	-
Lechin 1989	?	?	+	+	-	?	-
Leijon 1989	?	?	+	?	+	?	-
Lindstrom 1987	?	?	?	-	+	?	-
Nicol 1969	?	?	?	+	?	?	-
Rull 1969	?	?	+	-	+	?	-
Wilton 1974	?	?	+	-	-	?	-

**Size.** Treatment group sizes were small, ranging from a maximum of 12 to 66 (mean 33, median 33 for carbamazepine). Small studies can be associated with larger treatment effects than bigger studies (Counsell 1994; Moore 1998a; Moore 1998b; Nuesch 2010).

**Duration.** Studies were of generally of short duration, with individual treatment periods ranging from five-days in a straightforward cross-over study (Killian 1968) to 42 months in a partial cross-over study in which participants stayed on the



first treatment for a minimum of two weeks and switched only if or when treatment was 'unsatisfactory' (Nicol 1969). One study (Lechin 1989) used eight-week treatment periods and three studies (Campbell 1966; Gomez-Perez 1996; Leijon 1989) used four-week periods, with the remainder using 5 to 14 day periods. Chronic pain studies of six weeks or less have been shown to manifest greater treatment effects than those of eight weeks or more (Moore 2009b).

**Outcome.** A variety of different pain outcomes was reported, including average pain scores, raw individual pain scores (though not always complete), dichotomous outcomes such as the proportion with any improvement or benefit, including scores (like global impression of change) equivalent to IMMPACT outcomes of moderate or substantial benefit (Dworkin 2008); some studies gave little or no indication of how many patients benefited from treatment. Four studies reported only group mean pain scores (Jia 2006; Lechin 1989; Wilton 1974) or a measure of 'upgrading', rather than absolute pain scores or amount of change (Campbell 1966). Higher levels of benefit (e.g.  $\geq 50\%$  pain relief rather than any pain relief) result in higher NNTs (Moore 2009b).

None of the included studies mentioned how missing data were handled, for example using last observation carried forward or baseline observation carried forward imputation for participants who withdrew from the studies. Some studies may have analysed only those participants who completed the study, or both phases of a cross-over study.

Intention-to-treat analysis was not carried out and patients who dropped out of studies were not included in the analysis. This is likely to be the source of additional bias.

Exaggeration of treatment effects in cross-over trials compared with parallel group designs has been seen in some circumstances (Khan 1996), but it is unclear whether this is a general effect (Elbourne 2002). The predominance of cross-over trials in this review has to be considered as a possible source of additional bias. In these circumstances, caution is needed in interpreting the data as far as efficacy is concerned. In particular, meaningful comparison of efficacy with other interventions is not possible.

## Effects of interventions

See: [Summary of findings for the main comparison](#)

Ten studies were suitable for inclusion. Studies enrolled participants with trigeminal neuralgia, diabetic neuropathy, or post stroke pain. There were no studies investigating carbamazepine in other neuropathic pain conditions or in fibromyalgia. Details of results in individual studies are presented in [Appendix 4](#).

### Trigeminal neuralgia

Five studies of carbamazepine in trigeminal neuralgia were included. One of these (Killian 1968) also recruited some participants with other neuralgias; 30 of 42 participants had trigeminal neuralgia.

There was no first or second tier evidence of efficacy.

#### Third tier evidence.

Three studies were placebo-controlled (Campbell 1966; Killian 1968; Nicol 1969). Using dose titration to a maximum daily dose of 1000 mg, 19/27 participants had a complete or very good response

with carbamazepine compared with minimal or no response with placebo on five days' treatment in a subset of patients with trigeminal neuralgia (Killian 1968). Again using dose titration and a cross-over design, but to a maximum daily dose of 2400 mg, 15/20 participants randomised to initial carbamazepine had a good or excellent response after 14 days' treatment, compared with 6 of 24 reporting good or excellent response who started on placebo (Nicol 1969). There were too few data for analysis.

A study by Campbell 1966 reported results by the number of changes in the pain score; this study has been removed from the analyses in this version as the numbers presented in the paper are events rather than patient data. It had claimed a mean fall in maximum pain intensity of 58% after two weeks with carbamazepine 400 to 800 mg daily compared to 26% with placebo.

Two active controlled studies were included. Lindstrom 1987 compared carbamazepine (maximum tolerated dose) with tocainide (an antiarrhythmic drug; 20 mg/kg/day divided into three doses). All participants had baseline pain scores without treatment of  $\geq 4/10$ . There was no difference between the treatments; 7/12 and 6/12 participants treated with carbamazepine and tocainide respectively had mean pain scores of  $\leq 3/10$  (no worse than mild pain) in the last 10 days of a two-week treatment period. Only one participant responded to carbamazepine, but not tocainide.

Lechin 1989 compared carbamazepine (titrated to maximum 1200 mg/day) with pimozide (an antipsychotic drug; titrated to maximum 12 mg/day) over eight weeks. All 24 participants treated with pimozide, and 14/24 treated with carbamazepine in the first period of treatment "eventually improved", with maximal improvement after 6 weeks of treatment. Results for the second period of the cross-over study were similar.

### Diabetic neuropathy

Four studies evaluated carbamazepine in diabetic neuropathy (Gomez-Perez 1996; Jia 2006; Rull 1969; Wilton 1974).

There was no first or second tier evidence of efficacy.

#### Third tier evidence

Two studies were placebo controlled (Rull 1969; Wilton 1974). In a complicated three-way cross-over, Rull 1969 found that, using the top two levels of pain improvement (3 points or better out of 5), in the first two of three cross-over periods for each group, 17/30 improved with carbamazepine and 2/30 for placebo, over two weeks. The other study (Wilton 1974) reported only on preferences after one week of treatment with carbamazepine and placebo; 24/40 preferred carbamazepine, 14/40 preferred placebo, and 2/40 had no preference.

Two active controlled studies met the inclusion criteria. One compared carbamazepine 200 mg to a nortriptyline 10 mg plus fluphenazine 0.5 mg combination over four weeks (Gomez-Perez 1996). No significant difference was found between carbamazepine and the nortriptyline combination; both treatments improved paraesthesia and pain. Jia 2006 compared venlafaxine with carbamazepine over two weeks in 132 participants, with both drugs given at fixed and relatively low dose. Both drugs demonstrated effect with venlafaxine showing a somewhat larger mean effect.

## Post stroke pain

There was no first or second tier evidence.

### Third tier evidence

A cross-over study compared carbamazepine, amitriptyline, and placebo, with a treatment duration of four weeks for each (Leijon 1989). Global report of any improvement occurred in 10 of 15 on amitriptyline, 5 of 15 on carbamazepine, and 1 of 15 on placebo.

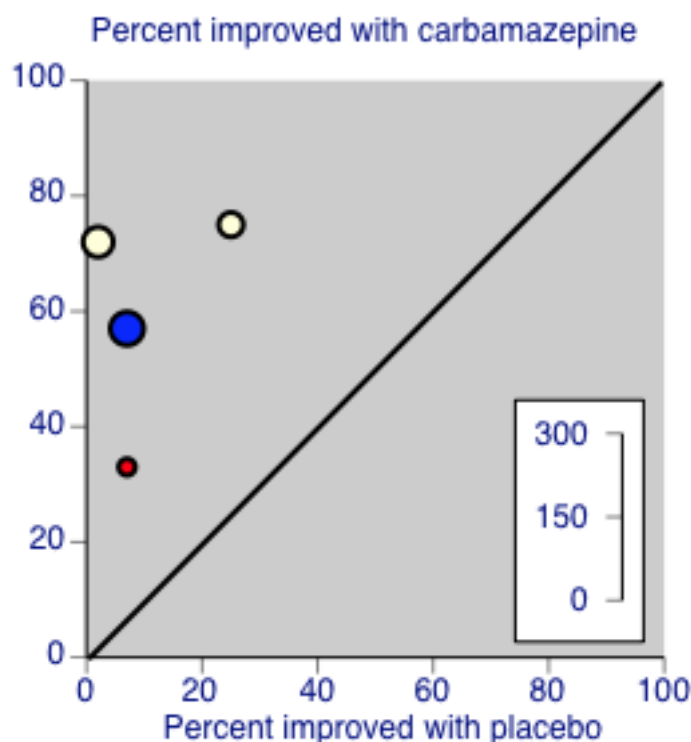
### Overall estimation of efficacy

Although we specified that we would analyse different pain conditions separately, because carbamazepine is such a widely

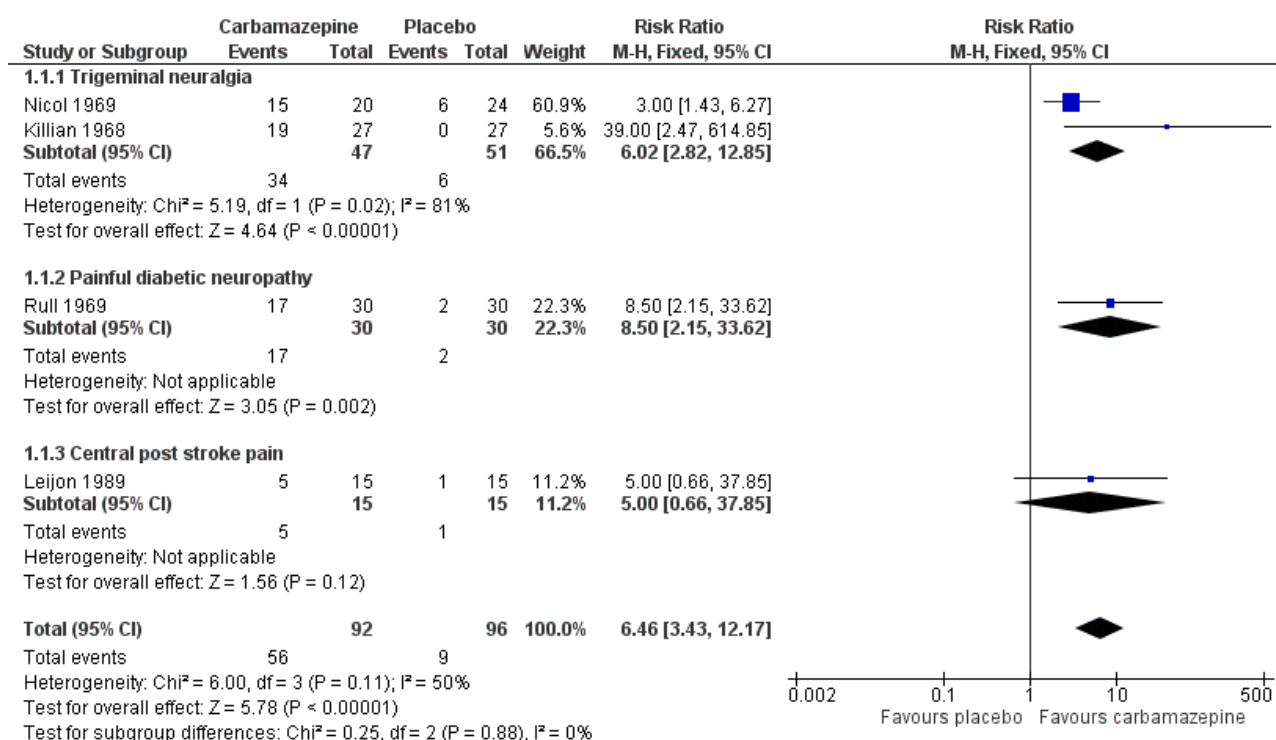
used drug for neuropathic pain (particularly trigeminal neuralgia) and because we found so little evidence, we did carry out a post-hoc analysis combining pain conditions to look for a direction of effect.

Four studies (188 participants) compared carbamazepine with placebo and provided dichotomous outcomes equivalent to the IMMPACT substantial improvement (Killian 1968; Leijon 1989; Nicol 1969; Rull 1969). Carbamazepine at any dose was consistently better than placebo (Figure 4) and overall 61% (56/92) of participants improved with carbamazepine compared with 9% (9/96) with placebo. The RR was 6.5 (3.4 to 12.2), and the NNT 1.9 (1.6 to 2.5) (Analysis 1.1; Figure 5).

**Figure 4. Four studies showing percentage improvement (any definition) with carbamazepine (any dose) and placebo. Size of the study is proportional to the size of the symbol (inset scale). Yellow symbols = trigeminal neuralgia, blue = painful diabetic neuropathy, red = post stroke pain**



**Figure 5. Forest plot of comparison: 1 Carbamazepine in neuropathic pain, outcome: 1.1 Any pain improvement.**



## Withdrawals

Eight studies provided information on adverse event withdrawals with carbamazepine (Campbell 1966; Gomez-Perez 1996; Killian 1968; Lechin 1989; Leijon 1989; Lindstrom 1987; Nicol 1969; Wilton 1974). In these studies, 8/268 (3%) of participants withdrew because of adverse events with carbamazepine, compared with 0/255 with placebo.

## At least one adverse event

Four studies provided information on participants experiencing at least one adverse event (Campbell 1966; Lechin 1989; Leijon 1989; Wilton 1974). Adverse event experience was more common with carbamazepine (66% of participants) than placebo (27%), RR 2.4 (1.9 to 3.2), NNH 2.6 (2.1 to 3.5).

## Serious adverse events

Serious adverse events were not reported consistently, and that included the absence of negative statements that there were no serious adverse events. Only one study (Gomez-Perez 1996) reported an adverse event as serious, a case of upper gastrointestinal bleeding thought to be associated with alcohol rather than carbamazepine. Rashes associated with carbamazepine were reported in two participants in Rull 1969; these may be considered serious because of association with Stevens-Johnson syndrome.

## Deaths

Four deaths occurred on treatment with carbamazepine, all in one study (Nicol 1969), which had the longest follow-up; two participants died suddenly, presumably of cardiovascular disease, one had a brain tumour, and one died of progressive debilitating disease.

## Specific adverse effects

Specific adverse events reported at high incidence (> 10%) included giddiness, dizziness, unsteadiness, and somnolence. These were not reported in sufficient detail to be combined, but the incidence of somnolence and dizziness was as high as 40-60% with carbamazepine.

## DISCUSSION

Much has been written about how to justify the use of our long-established medical interventions. While the randomised controlled trial (RCT) is the gold standard for the assessment of health care technologies and interventions (DOH 1992), buttressed by double blinding when the outcome measures are subjective (Colditz 1989; Schulz 1994; Turner 1994), the fact remains that many interventions are time-honoured rather than RCT-honoured. On whom then does the burden of proof fall? (Eddy 1993). The aim of this systematic review was to review the effectiveness and safety of the antiepileptic drug carbamazepine in the management of neuropathic pain and fibromyalgia. Since the first version of this review, gabapentin has become established as a treatment for neuropathic pain, and is now licensed for this indication in a number of countries. The problem is that there is very little good evidence to support the received wisdom regarding carbamazepine and its use in neuropathic pain or fibromyalgia generally, or even in trigeminal neuralgia, where response to carbamazepine has in the past been regarded as almost pathognomic.

More recent antiepileptic drugs have good evidence of effect, as with gabapentin (Moore 2011), pregabalin (Moore 2009a), or oxcarbazepine (Zhou 2013), or good evidence of lack of effect as with lamotrigine (Wiffen 2013b) and topiramate (Wiffen 2013c). An updated version of Gabapentin is currently awaiting



publication (April 2014) and an overview of these medicines titled 'Antiepileptic drugs for neuropathic pain and fibromyalgia-an overview of Cochrane reviews' has been recently published (Wiffen 2013a).

## Summary of main results

Carbamazepine generally provided better pain relief than placebo in a comparison that included three different chronic neuropathic pain conditions (trigeminal neuralgia, painful diabetic neuropathy, and central post stroke pain). There was some indication of pain improvement over mainly the short term, but with poorly defined outcomes, in fewer than 200 participants (less than a tenth of the number of participants available for one dose of pregabalin, for instance; (Moore 2009a)). The NNH for any adverse event was 4, though again reporting was neither consistent nor complete.

What we have is an indication that carbamazepine can produce good levels of pain relief for some patients with distressing chronic painful conditions.

## Overall completeness and applicability of evidence

The evidence is far from complete, and any assessment of applicability resides less with the evidence than the long experience of using the drug in neuropathic pain. The major problems with the amount and quality of the evidence available include:

- limited size, with all but one study involving fewer than 60 participants;
- short duration, with all but two studies being four weeks or less in treatment duration;
- inadequate outcomes, with inconsistent reporting not allowing outcomes equivalent to IMMPACT outcomes of at least moderate benefit to be assumed;
- incomplete outcome assessment, with studies reporting on completers only, or not reporting on imputation methods.

Poor quality reporting limited the ability to combine data, because many studies reported insufficient information, used a variety of different outcome measures, and several studies used variable dosing. Although the authors of the original reports were originally contacted by letter, not all of them replied, and of those who did, only Leijon 1989 was able to provide additional data.

Doses of carbamazepine used in some of the studies were small; Gomez Perez, for example, used 200 mg daily, which while effective in some is not effective in all (Taylor 1981). Dose escalation was rapid in some studies, potentially resulting in adverse effects. Although carbamazepine takes two to four days to achieve its maximum effect, auto induction of enzymes that metabolise the drug, which is complete at three weeks, often means that late dose increases are needed. These factors are largely ignored, and this limits the applicability of the available evidence.

These studies do not provide adequate information about adverse events, and in particular serious adverse events. This is of particular importance for serious cutaneous adverse events in some parts of the world. A strong genetic association between HLA-B\*1502 and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis has been shown in Han Chinese (Chung 2010), Indian (Mehta 2009), and Thai (Tassaneeyakul 2010) populations,

and Asian populations generally may be more susceptible. While the frequency of this allele is low in Europe, its frequency in Asian populations is 5-10% (Chung 2010). Carbamazepine is the most common causative agent for Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe (8% of total), rising to 26% in Taiwan, 36% in Malaysia and 28% in Singapore (Chung 2010).

There is also an interaction between carbamazepine and warfarin metabolism which can be of major clinical importance (Herman 2006). If treatment with carbamazepine cannot be avoided, patients taking warfarin should be frequently monitored, especially when initiating or stopping carbamazepine therapy.

## Quality of the evidence

Studies were small, short, and had inadequate definitions of benefit, plus incomplete reporting. For each of these there is evidence that they could be the source of systematic bias, and this significantly reduces the weight we can give such evidence as we have. In particular, it limits comparability of carbamazepine results with results for other interventions obtained from larger, longer, and better studies and meta-analyses.

In order to be sure that carbamazepine works in chronic painful conditions and to be confident of the magnitude of the effect, the ideal would be several large randomised double blind studies comparing carbamazepine at sensible doses with placebo, over 8 to 12 weeks, and using IMMPACT outcomes (perhaps at least moderate improvement or benefit) or their equivalent in each of several clinical conditions, as we have for pregabalin, for example (Moore 2009a). We actually have only one study of adequate duration; Lechin 1989 enrolled 59 participants with trigeminal neuralgia, had a quality score of 4 of 5, but reported only an undefined improvement for only 48 of 59 participants randomised (1 lost to follow-up and 10 protocol deviations).

## Potential biases in the review process

Criteria for assessing potential biases in chronic pain are becoming more stringent as new biases are being discovered (Moore 2010b; Moore 2012b). Potential biases in the review process derive from including studies with the potential for bias, though the review has sought to highlight the potential for bias when it occurs.

Using only criteria of sufficient stringency to avoid all these potential biases would reduce the pool of included studies to nil, which, given that carbamazepine is used to treat neuropathic pain, is less than helpful.

## Agreements and disagreements with other studies or reviews

The results of this review are generally in agreement with the previous version. We are not aware of any other systematic reviews specifically concerning carbamazepine, but a broad overview of interventions for neuropathic pain (Finnerup 2005) had a combined NNT for efficacy of 2.0 (1.6 to 2.5), similar to our estimate of 1.7 (1.5 to 2.0). The source of the small difference cannot be ascertained from details provided.

## AUTHORS' CONCLUSIONS

### Implications for practice

Carbamazepine is probably effective in some people with chronic neuropathic pain, but with major caveats. Only third tier evidence was available, which is subject to potentially major bias in favour of active therapy. No trial was longer than four weeks, or of good reporting quality, nor used outcomes equivalent to substantial clinical benefit. In these circumstances, caution is needed in interpretation, and meaningful comparison with other interventions is not possible. An overview of antiepileptics in neuropathic pain and fibromyalgia concluded that, among antiepileptic drugs, clinical trial evidence supports only the use of gabapentin and pregabalin in some neuropathic pain conditions (painful diabetic neuropathy, postherpetic neuralgia, and central neuropathic pain) and fibromyalgia (Wiffen 2013b).

The use of carbamazepine in neuropathic pain has stood the test of time in the clinic, but carbamazepine usually does not now feature in treatment algorithms, other than for the treatment of trigeminal neuralgia. Current guidance in the UK states 'Despite the lack of trial evidence, it is perceived by clinicians to be efficacious. Further research should be conducted as described in the table below.' (NICE 2013)

Medical students are often taught that a positive response to carbamazepine is 'diagnostic' for trigeminal neuralgia. Even the suspect evidence we have indicates that this is not the case, with perhaps just over half of participants with trigeminal neuralgia having a good response to carbamazepine. Clinically it appears that trigeminal neuralgia can become refractory to carbamazepine.

The usual clinical decision for chronic neuropathic pain is a choice between antidepressant and antiepileptic as first-line treatment, and there is insufficient evidence to support the use of carbamazepine as first line. In addition the need for laboratory monitoring and significant drug interactions with the use of

carbamazepine have discouraged the use of carbamazepine with the emergence of newer antiepileptic drugs, such as gabapentin and pregabalin.

### Implications for research

This review shows that there is still a need for large, high quality, long duration studies using sensible outcomes to establish relative effectiveness of different antiepileptics in chronic pain syndromes, and for comparisons of other treatments such as antidepressants with antiepileptics; appropriate trial designs have been suggested for this (Moore 2009c). The usefulness of such studies would be increased greatly by improvements in the quality of reporting, and particularly by use of clinically important end points rather than undefined improvement. Enriched enrolment randomised withdrawal studies have real potential (McQuay 2008).

For carbamazepine the particular interest lies in treating trigeminal neuralgia. For this condition, for all interventions, there have been only a handful of good quality studies reported. The major implication for research is therefore for trigeminal neuralgia as a specific condition, and using carbamazepine as an historically useful medicine to understand the parameters around the conduct of successful clinical trials in a debilitating and often poorly responding condition.

## ACKNOWLEDGEMENTS

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The Oxford Pain Relief Trust provided general institutional support for this update.

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Wiffen PJ, Derry S, Moore RA, McQuay HJ. Carbamazepine for acute and chronic pain in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 1. [DOI: [10.1002/14651858.CD005451.pub2](https://doi.org/10.1002/14651858.CD005451.pub2)]

\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Campbell 1966

Methods	Multicentre, randomised, double blind, placebo controlled, cross-over. Not enriched. Duration 8 weeks (4 two-week periods)
Participants	Trigeminal neuralgia
	N = 77 (but 7 excluded, 6 for logistic problems, one for a rash)

#### Carbamazepine for chronic neuropathic pain and fibromyalgia in adults (Review)

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**Campbell 1966** (Continued)

36 started on carbamazepine, 34 (report says 35 in one place) started on placebo

Age range 20 to 84 (mean 59) years. Male 34%

Interventions	CBZ 100 mg 4 x daily to 200 mg 3 x daily (1 centre), or 200 mg 4 x daily (2 centres)  Placebo  Order of treatment CBZ, P, CBZ, P or P, CBZ, P, CBZ
Outcomes	Pain intensity: 4 point scale to determine "upgrading"  Frequency of paroxysms and triggers  Adverse events  Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1, Total = 5  Geigy supplied tablets

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'random number lists'
Allocation concealment (selection bias)	Unclear risk	'neither patient nor doctor knowing the order of therapy given'
Blinding (performance bias and detection bias) Active and controlled appeared similar	Low risk	'placebo indistinguishable in appearance from active drugs'
Duration	High risk	2 week treatment period
Outcome	High risk	Upgrading not level of change
Incomplete outcome assessment	Unclear risk	Not stated
Size	High risk	Group size below 50

**Gomez-Perez 1996**

Methods	Randomised, double blind, double dummy, active controlled, cross-over (washout and phase 2 only). Duration: two 30-day treatment periods plus washout. Not obviously enriched
Participants	Adult patients with diabetic neuropathy - severe pain  N = 16  Age and sex not stated
Interventions	CBZ 300 mg to 600 mg daily

**Gomez-Perez 1996** (Continued)

Nortriptyline 10 mg plus fluphenazine 0.5 mg combination (3 to 6 tablets daily)

Dose increment over 3 days then stable to day 15 then double dose for next 15 days. 2 to 4 weeks washout then cross-over

Outcomes	Symptom intensity for pain and paraesthesia: Vertical VAS, 0 to 100  Withdrawals  Adverse events
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1, Total = 4  Geigy supplied the drugs

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'randomly assigned'
Allocation concealment (selection bias)	Unclear risk	No statement
Blinding (performance bias and detection bias) Active and controlled appeared similar	Low risk	'an identical placebo tablet of the comparing drug was given simultaneously with the active drug'. Double dummy design
Duration	Unclear risk	4 week treatment periods
Outcome	Low risk	At least 50% decrease of pain
Incomplete outcome assessment	Unclear risk	Not stated
Size	High risk	Group size below 50

**Jia 2006**

Methods	Randomised, double blind, double dummy, active control, parallel group. Not obviously enriched  Duration 14 days
Participants	Painful peripheral diabetic neuropathy  N = 132 (66 in each treatment group)  Age and sex not reported
Interventions	CBZ 100 mg twice daily  Venlafaxine 25 mg twice daily
Outcomes	Numerical pain intensity scores using 11 point Likert scale  Assessment of ADL, sleep and mood

## Jia 2006 (Continued)

Withdrawals

Adverse events

Notes Oxford Quality Score: R = 2, DB = 2, W = 1, Total = 5

### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'random sequence generated by computer'
Allocation concealment (selection bias)	Low risk	'sealed opaque envelopes'
Blinding (performance bias and detection bias) Active and controlled appeared similar	Low risk	Double dummy design. 'each patient took venlafaxine 25mg plus one dummy carbamazepine' or vice versa
Duration	High risk	14 days
Outcome	High risk	Mean data only, no responder analysis
Incomplete outcome assessment	Unclear risk	Not stated
Size	Unclear risk	66 in each treatment group

## Killian 1968

Methods Randomised, double blind, placebo controlled, partial cross-over. Duration 10 days (two 5-day periods). Not obviously enriched

Open follow-up, range 2 weeks to 36 months

Participants Trigeminal neuralgia N = 30, postherpetic neuralgia N = 6, other chronic neuralgia N = 6

36 of 42 participants studied double blind (24 of 30 with trigeminal neuralgia)

Age range 36 to 83 (mean 52) years, Female 66%

Interventions Carbamazepine dose titration 400 mg to 1 g daily  
Placebo

Outcomes Complete or very good pain response

Withdrawals

Adverse events

Notes Oxford Quality Score: R = 1, DB = 2, W = 1, Total = 4

Geigy sponsored

### Risk of bias

## Killian 1968 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'which were randomised'
Allocation concealment (selection bias)	Unclear risk	No statement
Blinding (performance bias and detection bias) Active and controlled appeared similar	Low risk	' a double blind technique . . . consisted of identical tablets'
Duration	High risk	5-day treatment period
Outcome	Low risk	Complete or very good pain response is equivalent to $\geq 50\%$ pain relief
Incomplete outcome assessment	Unclear risk	Not stated
Size	High risk	Groups size below 50

## Lechin 1989

Methods	Multicentre (4), randomised, double blind, active control, cross-over. Duration 24 weeks (4 week run-in, then two 8-week periods with 4-week washout). Not enriched  Open follow-up on pimozide
Participants	Trigeminal neuralgia. Duration of illness 8 to 17 (median 13) years  N = 59 randomised. Only 48 evaluated due to protocol violation and dropout  Age 48 to 64 (mean 59) years. Male 24, Female 24
Interventions	CBZ 300 mg to 1200 mg daily in 2 divided doses  Pimozide 4 mg to 12 mg daily in 2 divided doses  Step titration with daily doses as follows: CBZ and pimozide, days 1 to 4 300 mg and 4 mg respectively; days 5 to 9 600 mg and 6 mg respectively; days 10 to 14, 900 mg and 8 mg respectively; day 15 to end of treatment, 1200 mg and 12 mg respectively
Outcomes	Trigeminal neuralgia symptom score  Adverse events
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1, Total = 4  Grant from Foundation of the Institute for Experimental Medicine

### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'patients were randomly distributed in two groups'

**Lechin 1989** (Continued)

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Active and controlled appeared similar	Low risk	'all medications were administered in identical dark capsules'
Duration	Low risk	8 weeks treatment
Outcome	High risk	Average pain score
Incomplete outcome assessment	Unclear risk	Not stated
Size	High risk	Group size below 50

**Leijon 1989**

Methods	Randomised, double blind, double dummy, active control, cross-over. Duration 14 weeks (three 4-week periods with two 1-week washouts). No follow up. Partially enriched	
Participants	Central post stroke pain  N = 15  Age not reported, Male 12, Female 3	
Interventions	Stepped increase to final dose of CBZ 800 mg daily starting at 100 mg twice daily on day 1 then increasing on days 2, 6, 15, 18  Stepped increase to final daily dose of amitriptyline of 25 mg in the morning and 50 mg at night, starting at 12.5 mg twice daily on day 1 then increasing on days 2, 6, 15, 18	
Outcomes	Daily pain intensity (10 step verbal scale), post treatment global rating  Withdrawals	
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1, Total = 4  Sponsorship - Swedish public funds	

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'treatment given in randomised order'
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Active and controlled appeared similar	Low risk	'identical capsules containing active drug or lactulose(!) were given in double dummy technique'

**Leijon 1989** (Continued)

Duration	Unclear risk	4 week treatment periods
Outcome	Low risk	Individual pain response levels shown
Incomplete outcome assessment	Unclear risk	Not stated
Size	High risk	Group size below 50

**Lindstrom 1987**

Methods	Randomised, double blind, active control, cross-over (two 2-week periods - washout?). No follow up. Not enriched	
Participants	Trigeminal neuralgia N = 12 Age 41 to 78 years. Male 5, Female 7	
Interventions	CBZ to maximum tolerated dose Tocainide 20 mg/kg in 3 divided daily doses. Actual doses not reported	
Outcomes	TN pain score (summary of intensity, frequency and duration of attacks), 0 to 10 scale	
Notes	Oxford Quality Score: R = 1, DB = 1, W = 0, Total = 2 Sponsored by Folsam Research Foundation, Vivian L Smith Foundation	

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'randomised double blind technique'
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Active and controlled appeared similar	Unclear risk	Stated as double blind but no further information
Duration	High risk	2 week treatment
Outcome	Low risk	Probable that TN pain score $\leq 3/10$ equivalent to no worse than mild pain
Incomplete outcome assessment	Unclear risk	Not stated
Size	High risk	Group size below 50

## Nicol 1969

Methods	Randomised, double blind, placebo controlled, partial cross-over (successful first treatment period stayed on same treatment). Duration of treatment 2 to 42 months. Not obviously enriched.  Follow up 46 months.
Participants	Facial pain  N = 64, 54 with trigeminal neuralgia  Results presented on 44 TN only, due to insufficient follow up  Age not given. Male 21, Female 23
Interventions	CBZ dose titration 100 mg to 2.4 g daily  Placebo  Participants started on one treatment and increased dose to 8 tablets daily. At two weeks, if no satisfactory results, the second treatment was substituted  20 had carbamazepine only, 7 had placebo only; 17 had placebo then carbamazepine
Outcomes	Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1, Total = 3  Geighy supplied the tablets

### *Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'randomised investigation'
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Active and controlled appeared similar	Unclear risk	Stated as double blind but no further information
Duration	Low risk	long duration $\geq 12$ weeks
Outcome	Unclear risk	Probable that response was equivalent to $\geq 30\%$ pain relief
Incomplete outcome assessment	Unclear risk	Not stated
Size	High risk	Partial crossover means that groups size was below 50

## Rull 1969

Methods	Randomised, double blind, placebo-controlled, cross-over. Duration 6 weeks (three 2-week periods), no follow-up. Not obviously enriched
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## Rull 1969 (Continued)

Participants	Diabetic neuropathy  N = 30  Mean age 54 (21 to 81) years. Male 21, Female 30
Interventions	CBZ 200 mg to 600 mg daily  Placebo  Sequence CBZ, P, CBZ or P, CBZ, P
Outcomes	Participant reported change in symptoms (-5 to +5), reported as 5 categories  Adverse events
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1, Total = 4

### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'on a random basis, individuals were assigned'
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Active and controlled appeared similar	Low risk	'both drug and placebo were identical'
Duration	High risk	2 week treatment period
Outcome	Low risk	Improvement by +3 to +5 points probably equivalent to $\geq 30\%$ pain relief
Incomplete outcome assessment	Unclear risk	Not stated
Size	High risk	Group size below 50

## Wilton 1974

Methods	Randomised, double blind, placebo controlled, cross-over. Duration 4 weeks: 2-week washout then 7 days on each treatment period. No washout between treatments
Participants	Diabetic neuropathy of at least 3 months  N = 40  Mean age 56 (range 28 to 70) years. Female 75%
Interventions	Carbamazepine 200 mg 3 x daily  Placebo



**Wilton 1974** (Continued)

Outcomes	<p>Patient reported pain: 10 cm VAS scale</p> <p>Reported numbness, agitation, ability to sleep, depression and anxiety</p>
Notes	<p>Oxford Quality Score: R = 1, DB = 1, W = 0, Total = 2</p> <p>Geighy gave assistance</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'according to a pre-randomised balanced sequence'
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Active and controlled appeared similar	Low risk	'tegretol and an identical placebo dosage'
Duration	High risk	7 days treatment period
Outcome	High risk	Mean pain scores
Incomplete outcome assessment	Unclear risk	Not stated
Size	High risk	Group size below 50

ADL - activities of daily living; ADR - adverse drug reactions; AE - adverse effects; CBZ - carbamazepine; DN - diabetic neuropathy; NSAIDs - non steroidal anti-inflammatory drugs; QS - quality score; SE - side effect; TN - trigeminal neuralgia; vs - versus

**Characteristics of excluded studies** [ordered by study ID]

Study	Reason for exclusion
<a href="#">Crill 1973</a>	Review
<a href="#">Erzurumlu 1995</a>	Not RCT
<a href="#">Gerson 1977</a>	Open label
<a href="#">Harke 2001</a>	RCT but required pretreatment with spinal cord stimulation. 8 days treatment.
<a href="#">Keczkes 1980</a>	Acute condition. Pre-emptive treatment to reduce incidence of postherpetic neuralgia. Probably not blinded
<a href="#">Kudoh 1998</a>	Not RCT
<a href="#">Lloyd-Smith 1969</a>	Not randomised. Some patients crossed to placebo without consent
<a href="#">Rasmussen 1970</a>	Single blind

Study	Reason for exclusion
<a href="#">Rockliff 1966</a>	Fewer than 10 participants per treatment arm
<a href="#">Salinas 2012</a>	Pre-emptive treatment to reduce incidence or intensity of neuropathic pain
<a href="#">Shaikh 2011</a>	Not randomised or double blind
<a href="#">Swerdlow 1981</a>	Case series
<a href="#">Swerdlow 1984</a>	Review
<a href="#">Vilming 1986</a>	Fewer than 10 participants per treatment arm

### Characteristics of studies awaiting assessment *[ordered by study ID]*

#### [Badran 1975](#)

Methods	
Participants	
Interventions	
Outcomes	
Notes	Unable to locate paper

#### [Liebel 2001](#)

Methods	
Participants	
Interventions	
Outcomes	
Notes	Unable to locate paper

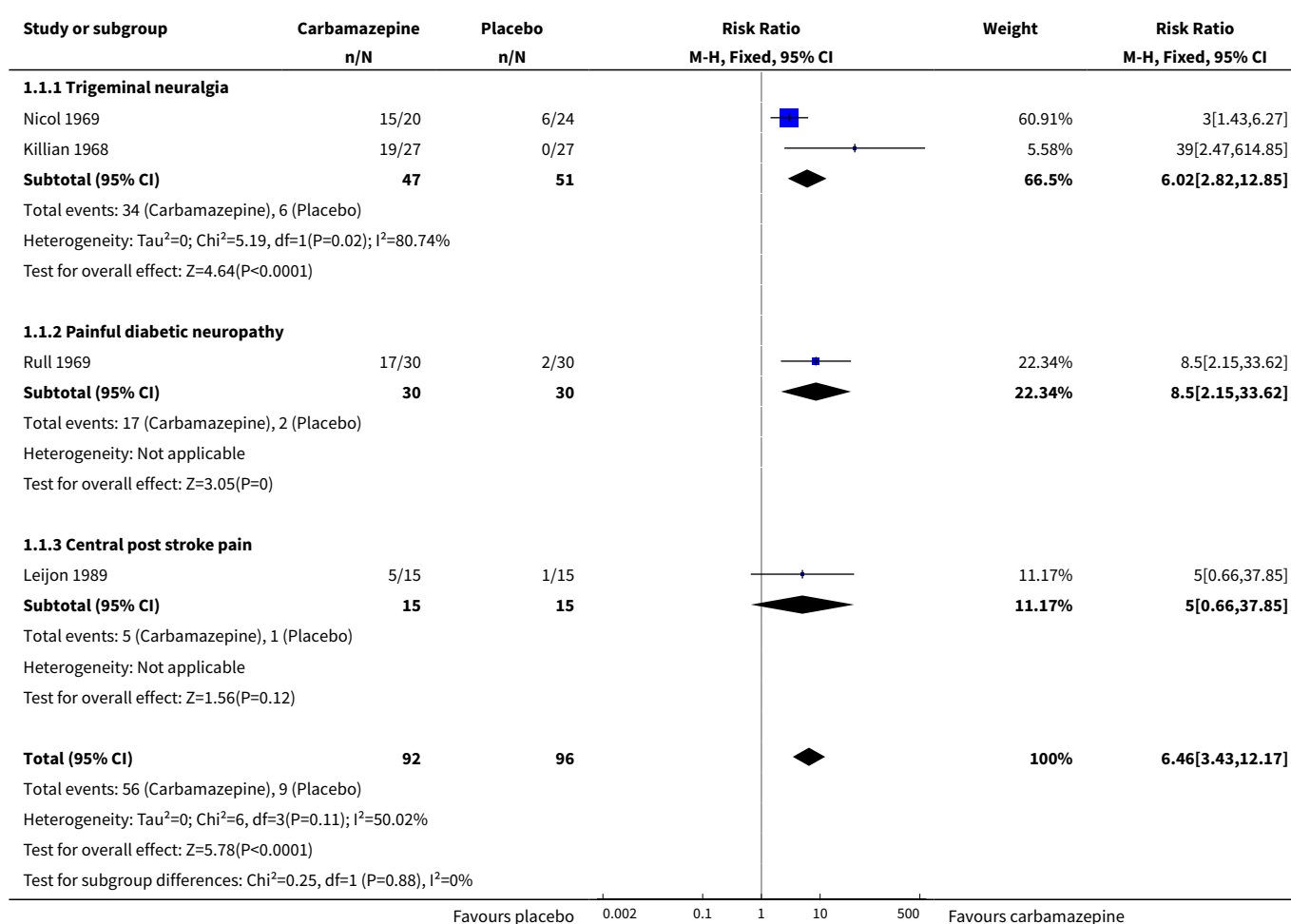
## DATA AND ANALYSES

### Comparison 1. Carbamazepine in neuropathic pain

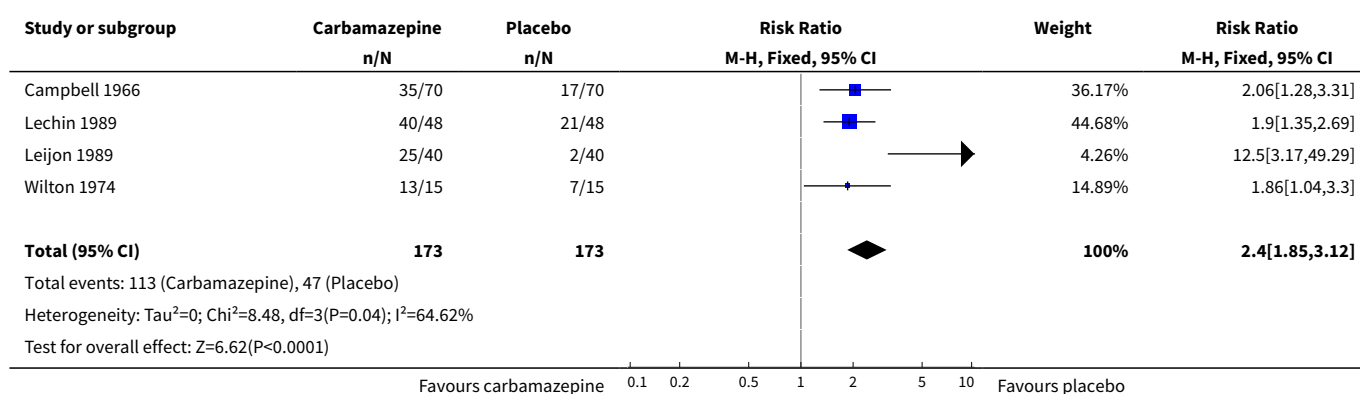
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Any pain improvement</a>	4	188	Risk Ratio (M-H, Fixed, 95% CI)	6.46 [3.43, 12.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Trigeminal neuralgia	2	98	Risk Ratio (M-H, Fixed, 95% CI)	6.02 [2.82, 12.85]
1.2 Painful diabetic neuropathy	1	60	Risk Ratio (M-H, Fixed, 95% CI)	8.5 [2.15, 33.62]
1.3 Central post stroke pain	1	30	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.66, 37.85]
<b>2 At least 1 adverse event</b>	<b>4</b>	<b>346</b>	<b>Risk Ratio (M-H, Fixed, 95% CI)</b>	<b>2.40 [1.85, 3.12]</b>

### Analysis 1.1. Comparison 1 Carbamazepine in neuropathic pain, Outcome 1 Any pain improvement.



## Analysis 1.2. Comparison 1 Carbamazepine in neuropathic pain, Outcome 2 At least 1 adverse event.



## APPENDICES

### Appendix 1. Methodological considerations for chronic pain

There have been several changes in how efficacy of both conventional and unconventional treatments is assessed in chronic painful conditions. The outcomes used today are better defined, particularly with new criteria of what constitutes moderate or substantial benefit (Dworkin 2008); older trials may only report participants with 'any improvement'. Newer trials tend to be larger, avoiding problems from the random play of chance. Newer trials also tend to be longer, up to 12 weeks, and longer trials provide a more rigorous and valid assessment of efficacy in chronic conditions. New standards have evolved for assessing efficacy in neuropathic pain, we are now applying stricter criteria for inclusion of trials and assessment of outcomes, and we are more aware of problems that may affect our overall assessment.

To summarise, some of the recent insights into studies in neuropathic pain and chronic pain more generally that make a new review necessary, over and above including more trials are:

1. Pain relief results tend to have a U-shaped distribution rather than a bell-shaped distribution, with participants either achieving very good levels of pain relief, or little or none. This is the case for acute pain (Moore 2005a), fibromyalgia (Straube 2010), and arthritis (Moore 2009b); in all cases average results usually describe the actual experience of almost no-one in the trial. Continuous data expressed as averages should be regarded as potentially misleading, unless it can be proved to be suitable. Systematic reviews now frequently report results for responders (Lunn 2009; Moore 2010a; Straube 2008; Sultan 2008).
2. This means we have to depend on dichotomous results usually from pain changes or patient global assessments. The IMMPACT group has helped with their definitions of minimal, moderate, and substantial improvement (Dworkin 2008). In arthritis, trials shorter than 12 weeks, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2009b); the effect is particularly strong for less effective analgesics. What is not always clear is how withdrawals are reported. Withdrawals can be high in some chronic pain conditions (Moore 2005b; Moore 2010b).
3. The proportion with at least moderate benefit can be small, falling from 60% with an effective medicine in arthritis, to 30% in fibromyalgia (Moore 2009b; Straube 2008; Sultan 2008). A Cochrane Review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009a). This indicates that different neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good grounds for doing so.
4. Finally, individual patient analyses indicate that patients who get clinically useful pain relief (moderate or better) have major benefits in many other outcomes, affecting quality of life in a major way (Hoffman 2010; Moore 2010c). Good response to pain predicts good effects for other troublesome symptoms like sleep, fatigue and depression.

These are by no means the only issues of trial validity that have been raised recently. A summary of what constitutes evidence in trials and reviews in chronic pain has been published (Moore 2010d). This review has attempted to address all of them, so that the review is consistent with current best practice.

### Appendix 2. Acute pain

#### Acute pain

A single study in acute herpes zoster examined whether carbamazepine reduced later development of postherpetic neuralgia (Keczkes 1980).

Comparing carbamazepine 400 mg daily with prednisolone (40 mg daily for 10 days reducing to zero over three subsequent weeks) in the management of acute herpes zoster, participants treated with prednisolone reported less pain and faster skin healing on average (3.7 weeks compared to 5.3 weeks) than those treated with carbamazepine. The study was probably not blinded. At two months 13 of 20 carbamazepine participants developed postherpetic neuralgia compared with 3 of 20 treated with prednisolone (Keczkes 1980).

No studies were found that investigated carbamazepine for the treatment of established acute pain after surgery, including third molar extraction.

### Appendix 3. Search strategies for this update

#### CENTRAL (Issue 7, 2012)

1. MeSH descriptor: [Carbamazepine] this term only (699)
2. (carbamazepin\* or neurotol or tegretol or amizepine or epitol):it,ab,kw (1393)
3. 1 or 2 (1393)
4. MESH descriptor PAIN explode all trees (30123)
5. (pain\* or discomfort\* or analgesi\*):it,ab,kw (68528)
6. 4 or 5 (73940)
7. 3 and 6 (528)
8. Limit 7 to Trials (463)

#### MEDLINE via Ovid (Jan 2010 to present)

1. Carbamazepine/ (907)
2. (carbamazepin\* or neurotol or tegretol or amizepine or epitol).mp. (1535)
3. 1 OR 2 (1535)
4. exp PAIN/ (45683)
5. (pain\* or discomfort\* or analgesi\*).mp. (90975)
6. 4 OR 5 (98866)
7. randomized controlled trial.pt. (65480)
8. controlled clinical trial.pt. (5580)
9. randomized.ab. (58837)
10. placebo.ab. (21707)
11. drug therapy.fs (251665)
12. randomly.ab. (38557)
13. trial.ti. (24394)
14. groups.ab (216456)
15. OR/7-14 (500200)
16. 3 AND 6 AND 15 (98)

#### EMBASE via Ovid (Jan 2010 to present)

1. Carbamazepine/ (8598)
2. (carbamazepin\* or neurotol or tegretol or amizepine or epitol).mp. (9186)
3. 1 or 2 (9186)
4. exp PAIN/ OR exp chronic pain/ OR exp neuropathic pain/ (227289)
5. (pain\* or discomfort\* or analgesi\*).mp. (246435)
6. 4 OR 5 (294514)
7. clinical trial.sh. (97620)
8. controlled clinical trial.sh. (48517)
9. randomized controlled trial.sh. (81717)
10. double-blind procedure.sh. (21886)
11. (clin\* adj25 trial\*) (6)
12. ((doubl\* or trebl\* or tripl\*) adj25 (blind\* or mask\*)) (3)
13. placebo\*.mp (79634)
14. random\*.mp (301145)
15. OR/7-14 (390020)

16.3 AND 6 AND 15 (652)

#### Appendix 4. Results in individual studies

Study  Particular issues	Maximum daily dose of carbamazepine Titration/fixed	Compara- tor  Numbers in trial	With- drawals	Efficacy	Adverse events (general)	Adverse events (specific)
<b>Trigeminal neuralgia</b>						
Cambell 1966	Carbamazepine 100 mg 4x daily to 200 mg 3x daily (1 centre) or 200 mg 4x daily (2 centres) in order C,P,C,P where C= carbamazepine, P= placebo. Placebo order P,C,P,C	Placebo  N = 70 total	7 with- drawals (1 rash, other logistic)  AE with- drawal Carba- mazepine 1/70 Placebo 0/70	58% of maximum pain relief with carba- mazepine, 26% maxi- mum with placebo	At least 1 AE Carba- mazepine 35/70 Placebo 17/70	Giddiness (30%) and unstead- iness (15%) most commonly re- ported
Killian 1968	Carbamazepine dose titration 400 mg to 1g / day	Placebo  N = 42 to- tal but 26 studies by double blind tech- nique, and 24/30 with trigemi- nal neural- gia studied by double blind tech- nique	AE with- drawal Carba- mazepine 3/30 Placebo 0/30	19/27 TN complete or very good response after 5 days. Placebo respons- es 'minimal or absent in all cases'.	At least 1 AE in 23/36 patients on carba- mazepine	With carba- mazepine 47% had dizzi- ness and some drowsiness
Lechin 1989	Step titration carba- mazepine 300 to 1200 mg daily Pimozide 4-12 mg daily in 2 divided doses. days 1-4 300 mg/d and 4 mg/d respectively; days 5-9 600 mg/d and 6mg/d days 10-14, 900 mg/d and 8 mg/d days 14 to end of treat- ment, 1200 mg/d and 12 mg/d	Pimozide  N = 59 68 recruit- ed, 59 ran- domised. 11 exclud- ed from analysis - 10 protocol violation, one did not return.	No AE with- drawals noted on either drug	TN symptom score. Pi- mozide lowered symp- tom score by 78% from baseline compared with 50% on carbamazepine. All patients "improved" on pimozide; 14/24 (58%) "improved" on carba- mazepine.	At least 1 AE Carba- mazepine 40/48 Pimozide 21/48	No data
Lindström 1987	Maximum tolerat- ed dose for carba- mazepine. 20 mg/kg in	Tocainide  N = 12	No AE with- drawals	Average TN pain score during final 10 days of treatment $\leq$ 3/10:	No data	No data

(Continued)

3 divided daily doses for  
tocainide. Actual doses  
not reported

noted on  
either drug

Carbamazepine 7/12, To-  
cainide 6/12.

TN score consisted of  
severity, frequency and  
duration of attacks.  
Tocainide and carba-  
mazepine produced sim-  
ilar improvement com-  
pared with 'no treat-  
ment'. No significant dif-  
ference between the ac-  
tive treatments

Nicol 1969	Carbamazepine dose titration 100 mg to 2.4 g/day. Placebo patients started on one treatment and increased dose until 8 tablets a day. At two weeks if no satisfactory results the second treatment was substituted.	Placebo  N = vari- able	AE with- drawal Carba- mazepine 2/37 Placebo 0/24	15/20 starting on car- bamazepine had good or excellent response (four point pain relief scale). 12/17 switched from placebo to carba- mazepine and 6/7 who continued on placebo had good or excellent re- sponse (6/24 who started on placebo).	Not con- cisely de- scribed	Death 4 deaths on Car- bamazepine, 2 with presumed car- diovascu- lar problems, one frontal lobe glioblastoma, and one of pro- gressive gener- alised debilitat- ing disease
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### Painful diabetic neuropathy

Gomez- Perez 1996	Carbamazepine (300mg to 600mg) vs nor- triptyline 10 mg/ fluphenazine 0.5 mg combination (3 to 6 tablets daily). Dose in- crement over 3 days then stable to day 15 then double dose for next 15 days. 2-4 weeks washout then crossover	Nortripty- line plus fluphenazine  N = 16	AE with- drawals 2/16 Carba- mazepine 0/16 Nor- triptyline	About 50% average pain relief on both treatments	No data	1 serious AE with Carbamazepine - upper gastroin- testinal bleeding, thought to be al- cohol induced  Constipation, nausea, epigas- tric pain with Carbamazepine  Dry mouth, dizzi- ness, constipa- tion, nausea with Nortripty- line  Mild and more frequent with Nortriptyline
Jia 2006	Venlafaxine 25mg twice a day or CBZ 100mg twice a day for 14 days	Venlafaxine  N = 132	AE with- drawals Carba- mazepine 2/66 Venlafax- ine 4/66	Mean pain intensity sig- nificantly reduced in both groups but greater in Venlafaxine. Mean pain score pre-intervention: 7  Mean pain score at 14 days: venlafaxine 2; car-	Severe AE Carba- mazepine 1/66 Venlafax- ine	Dizziness and somnolence (10%, 13%) with Carbamazepine, GI discomfort, dizziness and somnolence (18%, 14%, 12%) with Venlafaxine



(Continued)

				bamazepine 3.5 (from graph)		
Rull 1969	Carbamazepine 200 mg to 600 mg daily	Placebo N = 30	None mentioned	Pain intensity improved (any level) Carbamazepine 28/30 Placebo 19/30 0/30 worsened on carbamazepine versus 11/30 on placebo  Improvement equivalent to 50% pain relief in first period Carbamazepine 17/30 Placebo 2/30	No data	2 cutaneous rashes with carbamazepine.  "Untoward effects" frequent, but usually mild and transient. Somnolence (53%) dizziness (40%) and gait change (13%) most common AEs
Wilton 1974	Carbamazepine 200 mg three times a day	Placebo N = 40	No withdrawals noted	Preference for carbamazepine 24/40, placebo 14/40, no preference 2/40	At least 1 AE Carbamazepine 25/40 Placebo 2/40	Dizziness most common AE (21/40)

### Post stroke pain

Leijon 1989	Stepped increase to final dose of carbamazepine 800 mg daily starting at 100 mg 2x daily on day 1 then increasing on days 2, 6, 15, 18; amitriptyline started at 12.5 mg 2x daily on day one and increasing on the days above to 25 mg in the morning and 50 mg at night.	Placebo Amitriptyline N = 15	No AE with- drawals re- ported Carbamazepine 0/15 Amitriptyline 0/15 Placebo 0/15	Much improved or pain free Carbamazepine 5/15 Amitriptyline 2/15 Placebo 1/15  Improved, much improved or pain free Carbamazepine 10/15 Amitriptyline 5/15 Placebo 1/15	At least 1 AE Carbamazepine 13/14 Amitriptyline 14/15 Placebo 7/15  Moderate or severe AE Carbamazepine 5/14 Amitriptyline 2/15 Placebo 1/15	AEs mostly mild.  Vertigo, tiredness and gait disturbances most common with Carbamazepine, tiredness and dry mouth with Amitriptyline
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## WHAT'S NEW

Date	Event	Description
28 May 2019	Amended	Contact details updated.
27 February 2018	Review declared as stable	See <a href="#">Published notes</a>

## HISTORY

Review first published: Issue 3, 2005

Date	Event	Description
9 April 2014	Review declared as stable	This review will be assessed for updating in 2018.
29 August 2013	New search has been performed	New searches carried out. No new studies identified for inclusion, two studies identified, but excluded.  Methods updated to current practice and in line with other reviews of antiepileptic drugs for neuropathic pain and fibromyalgia. Five studies in earlier review now excluded on methodological grounds.
29 August 2013	New citation required but conclusions have not changed	Overall conclusions not changed, but strength of evidence downgraded.
27 June 2012	Amended	Contact details updated.
15 September 2011	Review declared as stable	The authors scanned the literature during August 2011 and were confident that this review would not need updating for at least five years.
8 February 2011	Amended	Contact details updated.
8 December 2010	New citation required but conclusions have not changed	This review update has been recorded for publication again as it was incorrectly published previously in July 2010. By republishing this review as a new citation we would like to draw the readers' attention to the fact that this review has been substantively updated with new current methods up to June 2010. The conclusions on the whole remain the same, however, the conclusions are now based on stronger methodology which were used to analyse all results. The review byline has also changed since the original publication in 2000.  The review was updated as follows: Review updated at first to December 2009 with searches re-run in June 2010 prior to publication. There are three new included studies and new parameters are considered for the chronic pain studies. Results have also been re-analysed.
8 December 2010	Amended	This review has been republished to draw attention to its revised methodology and more firm conclusions.
24 September 2010	Amended	Contact details updated.
1 June 2010	New search has been performed	Review updated Dec 2009 with searches re-run in June 2010. Three new included studies. New parameters considered for chronic pain studies. Re-analysis.
27 October 2008	Amended	Further minor Cochrane style changes made to this review as part of RevMan 5 conversion process.
7 July 2008	Amended	Converted to new review format.

Date	Event	Description
19 May 2005	Amended	This updated review on Carbamazepine was originally published as Anticonvulsant drugs for acute and chronic pain. At the third update in 2003, 12 new included studies were identified mainly of the newer anticonvulsants gabapentin and lamotrigine. In total the included studies provided data on six different medicines used in at least six identified neuropathic pain conditions. Issues of dose response and trial design added to the complexity. A decision was therefore taken to split this review into a number of smaller reviews each covering one medicine (chemical entity).

## CONTRIBUTIONS OF AUTHORS

PW registered the title, wrote the protocol, carried out searching and identified studies for inclusion. PW & RAM carried out data extraction, analysis, and drafting. All authors contributed to the final draft and approved the published version.

For this update, RAM and SD searched for additional studies. The updated Methods are taken from a template protocol for antiepileptics in neuropathic pain and fibromyalgia. SD, RAM and PW reassessed studies for inclusion. All authors contributed to the final draft and approved the published version.

PW will be responsible for updates.

## DECLARATIONS OF INTEREST

SD and PW have received research support from charities, government and industry sources at various times, but none relate to this review.

RAM has consulted for various pharmaceutical companies and received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions, including (in the past five years) AstraZeneca, Eli Lilly, Flynn Pharma, Furtura Medical, Grünenthal, GSK, Horizon Pharma, Lundbeck, Menarini, MSD, Pfizer, Reckitt Benckiser, Sanofi Aventis, Uro, Astellas, and Vifor Pharma.

## SOURCES OF SUPPORT

### Internal sources

- Oxford Pain Relief Trust, UK.

General institutional support for this update

### External sources

- No sources of support supplied

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The major difference between the original protocol and the 2010 update was the concentration on issues of methodological validity and bias that have emerged subsequently - namely on size, on duration, on outcome, and potentially on a dependence on cross-over designs. These are commented on and referenced in this updated review.

For this update we changed the title to reflect the clinical use of carbamazepine for pain relief, and to bring it in line with other reviews of antiepileptic drugs used to treat neuropathic pain and fibromyalgia; these reviews are included in an overview ([Wiffen 2013a](#)). As part of an ongoing drive to improve the standard of evidence in reviews we chose to exclude studies that were not double blind and did not have at least 10 participants per treatment arm. We also considered the implications of incomplete outcome assessment, and have analysed results according to the strength of the evidence (in three tiers).

The small amount of information relating to acute pain from the earlier review has been moved to [Appendix 2](#).

## NOTES

Review methods been substantially amended following a search for new trials up to June 2010. Methods used have been further amended in 2013 to bring it in line with current standards of evidence in chronic pain, and following new searches to bring the evidence up to date.

A restricted search in February 2018 did not identify any potentially relevant studies likely to change the conclusions. The authors and editors are confident that further research will not change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Analgesics, Non-Narcotic [adverse effects] [\*therapeutic use]; Carbamazepine [adverse effects] [\*therapeutic use]; Chronic Pain [\*drug therapy] [etiology]; Diabetic Neuropathies [\*drug therapy]; Fibromyalgia [\*drug therapy]; Neuralgia [drug therapy]; Randomized Controlled Trials as Topic; Stroke [complications]; Trigeminal Neuralgia [\*drug therapy]

### MeSH check words

Adult; Humans